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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/586,720	MAINA ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *12-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-9 and 11* is/are rejected.

7)☒ Claim(s) *4 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *July 20, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Election filed May 13, 2008.

Claims 1-30 are pending in the instant application.

Election/Restrictions

Applicant's election of Group I, claims 4 and 10, drawn to a method of preparing a hsiRNA mixture, comprising reacting a preparation of dsRNA with an effective amount of a mutant RNase III to produce the hsiRNA mixture, wherein the mutant RNase III is E38A, in the reply filed on May 13, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without** traverse (MPEP § 818.03(a)).

It is noted that claims 1-3, 5-9, and 11 links the inventions of Groups I-IV. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claims, claims 1-3, 5-9, and 11. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C.

121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

In this regard, claims 12-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Additionally, mutations E38T, E38W, or E65A as recited in claim 4 and mutant E65A as recited in claim 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. As noted above, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without** traverse.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-11 and mutation E38A have been examined on the merits.

Drawings

The drawings filed on June 20, 2006 are acknowledged and have been accepted by the Examiner.

Specification

Applicant's reference to priority in the first sentence of the specification is acknowledged. It is noted that this application is a § 371 application of international application number PCT/US2005/02029 filed on 21 January 2005, which claims priority from U.S. provisional application numbers 60/538,805 filed on 23 January 2004,

60/543,880 filed on 12 February 2004, and 60/572,240 filed on 18 May 2004.

Nucleotide Sequence Disclosures

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §1.821-1.825 for the reason(s) set forth below. The disclosure contains sequences which fall under the purview of 37 CFR 1.821 through 1.825 as requiring SEQ ID NOs., but which are not so identified. For example, see page 46, line 15. Applicant must fully comply with the sequence rules for any response to this action to be considered fully responsive.

Information Disclosure Statement

Applicant's information disclosure statement filed July 20, 2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12 are indefinite because the term "hsiRNA" is not clearly defined. Since abbreviations often have more than one meaning, it is suggested that inserting the full names of the RNA would overcome the instant rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Blaszczyk et al. (Structure, 2001 Vol. 9, Issue 12, pages 1225-1236, reference #CB on Applicant's Information Disclosure Statement filed July 20, 2006).

Claim 1 is drawn to a method of preparing a hsiRNA mixture, comprising reacting a preparation of dsRNA with an effective amount of a mutant RNase III to produce the hsiRNA mixture. Claims 2 and 3 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations wherein the mutant RNase III is contained in a magnesium or manganese buffer and wherein the mutant RNase III has a mutation in the position corresponding to E38 in *E. Coli* RNase III.

Blaszczyk et al. disclose an *Aquifex aeolicus* RNase III/Mg^{2+} dsRNA model in which hydrolysis events cleave the dsRNA into two strands of 11 nt, plus a 3' overhang

(see Figure 5a, for example). Blaszczyk et al. disclose that the *Aquifex aeolicus* RNase III was a site-directed mutant corresponding to residue E38 in *E. Coli* RNase III (see page 8, mid page and see Figure 1b, for example).

Therefore, Blaszczyk et al. anticipate claims 1-3.

Claims 1-3, 5-7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Sun et al. (Biochemistry, 2001 Vol. 40:14976-14984).

Claims 1-3 are as described above. Claim 5 is drawn to a method of forming an hsiRNA mixture, comprising combining a large dsRNA with a mutant RNase III for an effective time period so as to cleave the large dsRNA to form the hsiRNA mixture wherein (i) at least 90% of the large dsRNA is cleaved as determined by gel electrophoresis and ethidium bromide staining and (ii) at least 30% of the cleaved dsRNA which forms the hsiRNA mixture has a fragment size of 18-30 nt. Claims 6, 7, and 11 are dependent on claim 5 and includes all the limitations of claim 5 with the further limitations wherein the effective time period is about 1 min to 20 hours, wherein steps (i) and (ii) are achieved after 20 minutes; and wherein the large dsRNA has a length of at least 50 nt.

Sun et al. disclose the double-stranded-RNA processing activity of a truncated version of *E. Coli* RNase III lacking the dsRNA-binding domain. Specifically, Sun et al. disclose that *E. Coli* RNase III lacking the dsRNA-binding domain, in the presence of either Mg^{2+} or Mn^{2+} and for 25 or 30 minutes cleaved a 60 nt transcript dsRNA (see Figures 2 and 3, for example). Sun et al. also disclose that the *E. Coli* RNase III lacking

the dsRNA-binding domain cleaved at least 90% of its substrate (see Figure 4, for example). Sun et al. also disclose that following cleavage by *E. Coli* RNase III lacking the dsRNA-binding, reaction products were electrophoresed and visualized by phosphoimaging in which primary and secondary (1° + 2°) products were observed (see Figures 2 and 3, for example).

Therefore, Sun et al. anticipate claims 1-3, 5-7, and 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sun et al. (Biochemistry, 2001 Vol. 40:14976-14984).

Claim 5 is drawn to a method of forming an hsiRNA mixture, comprising combining a large dsRNA with a mutant RNase III for an effective time period so as to cleave the large dsRNA to form the hsiRNA mixture wherein (i) at least 90% of the large dsRNA is cleaved as determined by gel electrophoresis and ethidium bromide staining and (ii) at least 30% of the cleaved dsRNA which forms the hsiRNA mixture has a fragment size of 18-30 nt. Claims 8 and 9 are dependent on claim 5 and include all the limitations of claim 5 with the further limitations wherein steps (i) and (ii) are achieved after 5 hours or 10 hours, respectively.

Determining the scope and contents of the prior art

Sun et al. teach the double-stranded-RNA processing activity of a truncated version of *E. Coli* RNase III lacking the dsRNA-binding domain. Specifically, Sun et al. teach that *E. Coli* RNase III lacking the dsRNA-binding domain, in the presence of either Mg^{2+} or Mn^{2+} and for 25 or 30 minutes cleaved a 60 nt transcript dsRNA (see Figures 2 and 3, for example). Sun et al. also teach that the *E. Coli* RNase III lacking the dsRNA-binding domain cleaved at least 90% of its substrate (see Figure 4, for example). Sun et al. also teach that following cleavage by *E. Coli* RNase III lacking the dsRNA-binding, reaction products were electrophoresed and visualized by phosphoimaging in which primary and secondary (1° + 2°) products were observed (see Figures 2 and 3, for example).

Ascertaining the differences between the prior art and the claims at issue.

Sun et al. do not teach wherein steps (i) and (ii) are achieved after 5 hours or 10 hours.

According to general knowledge and understanding in the art, based upon standard enzyme kinetics, one of ordinary skill in the art would expect that the more time an enzyme is exposed to it's substrate, the more product would be produced.

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to devise a method of forming an hsiRNA mixture, comprising combining a large dsRNA with a mutant RNase III for an effective time period so as to cleave the large dsRNA to form the hsiRNA mixture wherein (i) at least 90% of the large dsRNA is cleaved as determined by gel electrophoresis and ethidium bromide staining and (ii) at least 30% of the cleaved dsRNA which forms the hsiRNA mixture has a fragment size of 18-30 nt using the teachings of Sun et al. It would have been obvious to have steps (i) and (ii) achieved after 5 hours or 10 hours using general knowledge in the pertinent art of biological science.

One of ordinary skill in the art would have been motivated to devise a method of forming an hsiRNA mixture, comprising combining a large dsRNA with a mutant RNase III for an effective time period so as to cleave the large dsRNA to form the hsiRNA mixture wherein (i) at least 90% of the large dsRNA is cleaved as determined by gel

electrophoresis and ethidium bromide staining and (ii) at least 30% of the cleaved dsRNA which forms the hsiRNA mixture has a fragment size of 18-30 nt since Sun et al. taught that such a method sheds light on the structure and function of *E. Coli* RNase III, an important enzyme which plays a key role in diverse prokaryotic and eukaryotic RNA maturation and degradation pathways. One of ordinary skill in the art would have been motivated to have steps (i) and (ii) achieved after 5 hours or 10 hours since based upon standard enzyme kinetics, one of ordinary skill in the art would expect that the more time an enzyme is exposed to it's substrate, the more product would be produced.

One of ordinary skill in the art would have had a reasonable expectation of success of devising a method of forming an hsiRNA mixture, comprising combining a large dsRNA with a mutant RNase III for an effective time period so as to cleave the large dsRNA to form the hsiRNA mixture wherein (i) at least 90% of the large dsRNA is cleaved as determined by gel electrophoresis and ethidium bromide staining and (ii) at least 30% of the cleaved dsRNA which forms the hsiRNA mixture has a fragment size of 18-30 nt since Sun et al. taught the successful use and design of such a method to elucidate the structure and function of *E. Coli* RNase III. One of ordinary skill in the art would have had a reasonable expectation of success of having steps (i) and (ii) achieved after 5 hours or 10 hours since the more time an enzyme is exposed to it's substrate, the more product would be produced was general knowledge known in the art at the time of filing. Therefore, one of ordinary skill in the pertinent art would have reasonably expected to have been able to achieve the instantly recited steps after 5 hours or 10 hours in view of that general knowledge.

Based on the teachings of Sun et al., a person of ordinary skill has good reason to pursue claims 5, 8, and 9 within his or her technical grasp. Since this leads to anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Conclusion

Claims 4 and 10 are objected to as containing nonelected subject matter, but would be allowable if rewritten to exclude the nonelected subject matter. Claim 4 is considered to be free of the prior art since the prior art does not teach or fairly suggest a method of preparing a hsiRNA mixture, comprising reacting a preparation of dsRNA with an effective amount of a mutant RNase III to produce the hsiRNA mixture, wherein the mutant RNase III is E38A. Claim 10 is considered to be free of the prior art since the prior art does not teach or fairly suggest a method of forming an hsiRNA mixture, comprising combining a large dsRNA with a mutant RNase III for an effective time period so as to cleave the large dsRNA to form the hsiRNA mixture wherein (i) at least 90% of the large dsRNA is cleaved as determined by gel electrophoresis and ethidium bromide staining and (ii) at least 30% of the cleaved dsRNA which forms the hsiRNA mixture has a fragment size of 18-30 nt, wherein the mutant RNase III is E38A.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758.

The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

July 15, 2008
/Terra Cotta Gibbs/